

REMARKS

Upon entry of this second preliminary amendment, claims 1, 8, 16, 18, 21, 24-25, 27, and 31-45 are in this application. New claims 32-45 are supported throughout the specification and by original claims 2-7, 9-15, 17, 19-20, 22-23, 26, and 28-30, respectively, and have eliminated most multiple dependencies. No new matter is added by this preliminary amendment.

The attached Abstract of the Disclosure is supported throughout the specification.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached Appendix A is captioned "**Version With Markings to Show Changes Made**".

Attached hereto is a clean copy of all of the pending claims. The attached Appendix B is captioned "**Clean Copy of Pending Claims Without Markings**".

Applicants respectfully request consideration of the pending claims.

The Director of the U. S. Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees to our Deposit Account No. 08-3040.

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**Appendix A**  
**Version with Markings to Show Changes Made**

**In the specification:**

Page 1, line 3, before "Field of the Invention", insert the following new paragraph:

**Cross-Reference to Related Applications**

This is a 371 of PCT/CA00/00258, filed March 9, 2000, which claims the benefit of the priorities of U. S. Patent Application No. 60/144,919, filed July 21, 1999, now abandoned, U. S. Patent Application No. 60/127,386, filed April 1, 1999, now abandoned, and U. S. Patent Application No. 60/124,260, filed March 11, 1999, now abandoned.

**In the claims:**

Claim 8 has been amended as follows:

8. (Amended) An isolated ~~KLK-L1~~ protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 2, ~~or~~ 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, and 67.

Claim 16 has been amended as follows:

16. (Amended) A protein prepared ~~in accordance with~~ by the method of claim ~~15~~ 37.

Claim 18 has been amended as follows:

18. (Amended) ~~An~~ The antibody ~~as claimed in~~ according to claim ~~17~~ 38 labeled with a detectable substance and used to detect the protein in biological samples, tissues, and cells.

Claim 21 has been amended as follows:

21. (Amended) A method ~~as claimed in~~ according to claim 20 40 wherein the condition is cancer.

Claim 24 has been amended as follows:

24. (Amended) A method for detecting a nucleic acid molecule encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, or 67 in a biological sample comprising the steps of:

- (a) hybridizing a nucleic acid molecule of claim 2 32 to nucleic acids of the biological sample, thereby forming a hybridization complex; and
- (b) detecting the hybridization complex wherein the presence of the hybridization complex correlates with the presence of a nucleic acid molecule encoding the protein in the biological sample.

Claim 27 has been amended as follows:

27. (Amended) A method ~~as claimed in~~ according to claim 26 44 wherein the condition is cancer.

Claim 31 has been amended as follows:

31. (Amended) A transgenic animal assay system which provides a model system for testing for an agent that reduces or inhibits a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein associated pathology comprising:

- (a) administering the agent to a transgenic non-human animal as claimed in claim 26 43; and
- (b) determining whether said agent reduces or inhibits a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein associated pathology in the transgenic non-human animal relative to a transgenic non-human animal of step (a) which has not been administered the agent.

**Appendix B****Clean Copy of Pending Claims Without Markings**

1. An isolated KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 nucleic acid molecule of at least 30 nucleotides which hybridizes to SEQ ID NO: 1, 13, 21, 43, 56, or 65, respectively, or the complement of SEQ ID NO: 1, 13, 21, 43, 56, or 65, under stringent hybridization conditions.

8. An isolated protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, and 67.

16. A protein prepared by the method of claim 37.

18. The antibody according to claim 38 labeled with a detectable substance and used to detect the protein in biological samples, tissues, and cells.

21. A method according to claim 40 wherein the condition is cancer.

24. A method for detecting a nucleic acid molecule encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, or 67 in a biological sample comprising the steps of:

- (a) hybridizing a nucleic acid molecule of claim 32 to nucleic acids of the biological sample, thereby forming a hybridization complex; and
- (b) detecting the hybridization complex wherein the presence of the hybridization complex correlates with the presence of a nucleic acid molecule encoding the protein in the biological sample.

25. A method as claimed in claim 24 wherein nucleic acids of the biological sample are amplified by the polymerase chain reaction prior to the hybridizing step.

27. A method according to claim 44 wherein the condition is cancer.

31. A transgenic animal assay system which provides a model system for testing for an agent that reduces or inhibits a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein associated pathology comprising:

(a) administering the agent to a transgenic non-human animal according to claim 43; and

(b) determining whether said agent reduces or inhibits a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein associated pathology in the transgenic non-human animal relative to a transgenic non-human animal of step (a) which has not been administered the agent.

32. The isolated nucleic acid molecule according to claim 1 which comprises:

(i) a nucleic acid sequence encoding a protein having substantial sequence identity with an amino acid sequence of a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein as shown in SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, or 67, respectively;

(ii) a nucleic acid sequence encoding a protein comprising an amino acid sequence of a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein as shown in SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, or 67, respectively;

(iii) nucleic acid sequences complementary to (i);

(iv) a degenerate form of a nucleic acid sequence of (i);

(v) a nucleic acid sequence capable of hybridizing under stringent conditions to a nucleic acid sequence in (i), (ii) or (iii);

(vi) a nucleic acid sequence encoding a truncation, an analog, an allelic or species variation of a protein comprising an amino acid sequence of a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein as shown in SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, or 67, respectively; or

(vii) a fragment, or allelic or species variation of (i), (ii) or (iii).

33. The isolated nucleic acid molecule according to claim 1 which comprises:

(i) a nucleic acid sequence comprising the sequence of SEQ ID NO: 1, 13, 21, 43, 56, or 65 wherein T can also be U;

(ii) nucleic acid sequences complementary to (i), preferably complementary to the full nucleic acid sequence of SEQ ID NO: 1, 13, 21, 43, 56, or 65;

(iii) a nucleic acid capable of hybridizing under stringent conditions to a nucleic acid of (i) or (ii) and preferably having at least 18 nucleotides; or

(iv) a nucleic acid molecule differing from any of the nucleic acids of (i) to (iii) in codon sequences due to the degeneracy of the genetic code.

34. A regulatory sequence of an isolated nucleic acid molecule of claim 32 fused to a nucleic acid which encodes a heterologous protein.

35. A vector comprising a nucleic acid molecule of claim 32.

36. A host cell comprising a nucleic acid molecule of claim 32.

37. A method for preparing a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, and 67 comprising:

- (a) transferring a vector of claim 35 into a host cell;
- (b) selecting transformed host cells from untransformed host cells;
- (c) culturing a selected transformed host cell under conditions which allow expression of the protein; and
- (d) isolating the protein.

38. An antibody having specificity against an epitope of a polypeptide or protein of claim 8.

39. A probe comprising a sequence encoding a protein of claim 8 or a part thereof.

40. A method of diagnosing and monitoring conditions mediated by a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66, and 67 by determining the presence of a nucleic acid molecule of claim 1 encoding the protein or determining the presence of said protein.

41. A method for identifying a substance which associates with a protein of claim 8 comprising:

- (a) reacting the protein with at least one substance which potentially can associate with the protein, under conditions which permit the association between the substance and protein; and
- (b) removing or detecting protein associated with the substance, wherein detection of associated protein and substance indicates the substance associates with the protein.

42. A method for evaluating a compound for its ability to modulate the biological activity of a protein of claim 8 comprising providing a known concentration of the protein with a substance which associates with the protein and a test compound under conditions which permit the formation of complexes between the substance and protein, and removing and/or detecting complexes.

43. A method of treating a condition mediated by a protein that comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 3, 14, 22, 23, 44, 45, 57, 58, 59, 60, 66 and 67 comprising administering an effective amount of a composition selected from the group consisting of:

- (a) an antibody having specificity against an epitope of said protein; and
- (b) a substance or compound identified by the method of one of claims 41 or 42.

44. A composition comprising a compound selected from the group consisting of:

- (a) a nucleic acid molecule of claim 1;
  - (b) a protein of claim 8; or
  - (b) a substance or compound identified by the method of one of claims claim 41 or 42,
- said composition further comprising a pharmaceutically acceptable carrier, excipient or diluent.

45. A transgenic non-human mammal which does not express a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein of claim 8, resulting in a KLK-L1, KLK-L2, KLK-L3, KLK-L4, KLK-L5, or KLK-L6 protein associated pathology, respectively.